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APPEAL BRIEF

Appellant : Shigeura et al.
App. No : 09/908,994
Filed : July 17, 2001
For : APPARATUS AND METHOD FOR
SPECIFIC RELEASE OF CAPTURED
EXTENSION PRODUCTS
Examiner : Bradley L. Sisson
Art Unit : 1634

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Sir:

In accordance with the Notice of Appeal filed August 24, 2007, Appellant submits this
Appeal Brief. Appellants request a one-month extension of time.

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I. REAL PARTY IN INTEREST

The real party in interest in this appeal is the assignee of this application, Applera Corporation.

II. RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any related appeals or interferences.

III. STATUS OF CLAIMS

Claims 21-38 are currently pending and are the subject of this Appeal. Claim 21 is the only independent claim. All of the pending claims stand finally rejected under a single asserted ground of obviousness, as detailed below. Claims 1-20 have been cancelled. The claims are attached hereto as Appendix A.

IV. STATUS OF AMENDMENTS

The claims before the Board appear as they were submitted in the Response dated July 24, 2007 and acknowledged as entered in the Advisory Action having a notification date of August 9, 2007. No further amendments were made to the claims after the Advisory Action. The pending claims are attached hereto as Appendix A.

V. SUMMARY OF CLAIMED SUBJECT MATTER

In general, the current claims are directed to a method that allows for the isolation of one or more different polynucleotides from a mixture in a concurrent manner via the use of a device comprising a plurality of solid supports that are arranged serially. The method allows for the separation of numerous polynucleotides and for the simultaneous elution of the separated polynucleotides, even though there is a single flow path. For example, by running a mixture containing 3 different polynucleotide species through a flow path having three different solid supports (each with a specific capture agent to bind to one of the polynucleotide species), the

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three different polynucleotides can be separated from one another along the flow path. Following this, one or more of the solid supports can be heated, allowing for the selective separation and elution of one or more of the polynucleotide species. In various embodiments, this method can be employed to achieve numerous advantageous results, some of which are outlined on page 25, line 17 to page 26, line 8 of the specification. The following denotes the claims being separately argued in the present appeal and some exemplary support for the elements in the claims (**in bold**).

21. A method for isolating one or more different-sequence polynucleotides from a mixture, the method comprising: **(page 28, lines 13 and 14)**

(a) flowing the mixture through a flow path (**FIG. 1, 14**) containing a plurality of solid supports (**FIG. 1, 22**) which are located in series in the flow path, such that the mixture flows serially through each of the plurality of solid supports, (**FIG. 1**) each support having bound thereto a sequence-specific capture agent complementary to a different-sequence polynucleotide, under conditions effective to specifically bind different-sequence polynucleotides to corresponding sequence-specific capture agents on one or more of the supports, **(page 28, lines 15-19)**

(b) after step (a), releasing bound polynucleotides from a selected support by altering a physical property of that support while leaving unaltered the same physical property of at least one other of the supports, wherein the physical property is temperature **(page 28, lines 20-22 and FIG. 7)**, and wherein said releasing is accomplished by heating a first solid support; and **(page 28, lines 26)**

(c) eluting the released polynucleotides through the flow path such that the eluted polynucleotides can be isolated in separated form. **(page 28, lines 23 and 24)**

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22. The method of claim 21, wherein said altering further comprises selectively heating a second solid support to release bound polynucleotides therefrom, to allow preferential elution of the polynucleotides released from the second solid support. **(page 29, lines 1-3)**

23. The method of claim 22, wherein heating of the first and second supports is performed simultaneously, and the polynucleotides released thereby are eluted in separate form, without mixing with each other. **(Original Claim 14, page 29, lines 5-7)**

30. The method of Claim 21, wherein all of the mixture flows through every one of the solid supports as the mixture proceeds down the flow path. **(FIG. 1 and FIG. 3)**

31. The method of Claim 21, wherein the solid support has an external surface and the flow path is defined by a structure having an internal surface, and wherein the external surface of the solid support abuts the internal surface of the flow path so that the mixture flows through the solid support in order to proceed down the flow path. **(page 8, line 25 to page 9, line 5, FIG. 1 and FIG. 3)**

32. The method of Claim 21, wherein the solid support has an external surface and the flow path is defined by a structure having an internal surface, wherein the external surface of the solid support is immediately surrounded by the internal surface of the structure defining the flow path. **(page 8, line 25 to page 9, line 5, FIG. 1 and FIG. 3)**

33. The method of Claim 21, wherein the solid support has an external surface and the flow path is defined by a structure having an internal surface, wherein the structure defining the

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flow path is a cylindrical tube made of heat-shrinkable plastic, and wherein the heat-shrinkable plastic immediately surrounds the external surface of the solid support. (page 8, line 25 to page 9, line 5, **FIG. 1 and FIG. 3**)

35. The method of Claim 34, wherein the column is a cylindrical column. (**FIG. 1-4**)

36. The method of Claim 35, wherein the solid support is a cylindrically shaped frit. (**FIG. 3, 22**)

37. The method of Claim 36, wherein an external surface of the cylindrically shape frit is immediately surrounded by an internal surface of the column so that all of the mixture flows through the solid support in order to proceed down the flow path. (page 8, line 25 to page 9, line 5, **FIG. 1 and FIG. 3**)

Appellants reserve the right to separately argue individual claims in subsequent continuing applications, with respect to the patentability of various dependent features not addressed herein.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The sole issue in the Final Office Action is whether all of the pending claims are obvious over the Examiner's proposed combination of Zanzucchi et al. (U.S. Pat. No. 5,593,838) in view of Okano et al. (5,607,646) and Brenner (U.S. Pat. No. 5,962,228).

VII. ARGUMENT

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The Examiner's Asserted Rejections Regarding Independent Claim 21

The Examiner has asserted that Zanzucchi discloses a method of isolating polynucleotides from a mixture via a serial array of wells where the wells include beads that can have DNA material bound to their surface and the wells can be heated and cooled. The Examiner has asserted that Okano teaches the use of heating and electric fields for elution of specific polynucleotides and that Brenner teaches an array formed of microparticles having tag components. The Examiner has asserted the following:

It would have been obvious...to have combined the microparticles of Brenner in the individual cells of the array of Okano with the series of wells/array of Zanzucchi et al., whereby the device would be used in a polynucleotide assay whereby specific binding reactions can take place at selected supports and eluted from same, and that the mixture would flow in a serial fashion through each of the solid supports. (Final Office Action, page 6).

Appellants respectfully disagree.

Legal Requirements for Establishing a Showing of Obviousness

The Court's recent decision in *KSR* reaffirmed the importance of the Graham factors in determining obviousness. The factors include four factual inquires that must be performed. One must (A) determine the scope and content of the prior art, (B) ascertain the differences between the prior art and the claims in issue, (C) resolve the level of ordinary skill in the pertinent art, and (D) evaluate evidence of secondary considerations. (*Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966)). The Examiner bears the initial burden to establish and support a *prima facie* case of obviousness.¹ To establish a *prima facie* case of obviousness, there must be some reason or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify or combine the references.² Furthermore, to establish a *prima*

¹ See *In re Rinehart*, 531 F.2d 1048, 189 U.S.P.Q. 143 (C.C.P.A. 1976).

² See *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). "The references themselves, not the invention itself, must provide some teaching whereby the appellant's combination would have

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facie case of obviousness, all the claim limitations must be taught or suggested by the prior art.³ Finally, even once a *prima facie* case of obviousness is established, it can be rebutted in situations in which the art taught away from the claimed combination.⁴

Deficiencies in the Rejections.

As explained in detail below, the cited art does not teach all of the elements in the claims and lacks sufficient scope and content to make the claimed combination obvious. Additionally, the various differences between the cited art and the claimed invention are significant and meaningful. In fact, some of the cited art actually teaches away from the Examiner's proposed modifications and combinations of the elements of the cited art, further emphasizing the differences and demonstrating strong evidence of nonobviousness. Finally, the Examiner's proposed reasons to combine the various references are faulty and even legally improper in various respects. As such, Appellants submit that the claimed invention is nonobvious. Each of these issues is addressed in more detail below. Following this analysis, Appellants have summarized the clear legal errors and factual mistakes made by the Examiner in the most recent Final Office Action and in the Advisory Action of August 9, 2007 and then address the nonobviousness of some of the additional dependent claims.

been obvious." *In re Forman*, 933 F.2d 982 (Fed. Cir. 1991); *Heidelberger Druckmaschinen AG v. Hantscho Commercial Products, Inc.*, 21 F.3d 1068 (Fed. Cir. 1993). See also, (*KSR Intl. v. Teleflex Inc.* (U.S. Supreme Court, April 2007)).

³ See *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

⁴ The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986), and *In re Geisler*, 116 F.3d 1465, 1471, 43 U.S.P.Q.2d 1362, 1366 (Fed. Cir. 1997)).

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A. The Cited References do not Teach all of the Recited Elements

The References do Not Teach the Recited Step of “(b) after step (a)...” in Claim 21

The Examiner has asserted that Zanzucchi discloses using an array of wells in serial fluid connection. Appellants acknowledge that one embodiment taught in Zanzucchi includes a serial arrangement of wells. However, what the Examiner has ignored is that the presently claimed method does not recite simply flowing a mixture into a series of “wells” where binding, release, and elution occur at some random point during the process. Rather, Claim 21 recites a method of flowing the mixture through each of the plurality of solid supports before one releases bound polynucleotides from the selected supports. Basically, this means that the mixture flows through all of the relevant solid supports (where each capture agent in the plurality of supports can bind to a polynucleotide that may be present in the sample) before one commences step (b). Appellants note that this order of occurrence is literally recited in the claim.

In contrast, in the method described in Zanzucchi (and thus the Examiner’s proposed combination), the mixture is moved into a first well (which would contain a single “solid support” in the Examiner’s proposed combination), one operates on that mixture (e.g., heating etc.), and then the mixture is moved into a second well, where one can perform another operation. This is the method that Zanzucchi teaches in regard to a single channel going through a set of serially arranged wells.⁵

Importantly, in Zanzucchi, the mixture to be operated upon is in a single well at any given time and is not manipulated so that various fractions of a sample are located in one well and other parts in a second well in series with the first. In particular, Zanzucchi teaches that each of the wells allows for a subsequent action upon a product from the previous well, suggesting that

⁵ See, e.g., the entire specification and figures, e.g., FIG. 2, FIG. 6A, “[t]he sample is treated sequentially in a series of wells...” (col. 4, lines 35-54) and Example 1 (Col. 8, line 66 to col. 11, line 2)

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Zanzucchi's method involves the stepwise action upon a single evolving product (see, e.g., (col. 4, lines 35-54) “[t]he sample is treated sequentially in a series of wells...” and Example 1, Col. 8, line 66 to col. 11, line 2 (in which blood cells are collected and lysed in a first well, the DNA from the cells transferred to a second well for DNA amplification, and hybridized in a third well for detection via a photodetector)). This is reemphasized by Zanzucchi's teaching that, in those wells in which heating is to occur, the reaction mixture has be held and sealed within the well (see, e.g., col. 9, lines 34-54) to prevent the mixture from leaving the well. Zanzucchi's stepwise approach is very different from the claimed method, in which the initial mixture if flowed through a plurality of solid supports prior to altering a physical property of any given support.

For direct comparison, Appellants note that Zanzucchi's method involves flowing a mixture into one well (which, according to the Examiner's proposal would contain a first substrate), allowing binding, sealing the well, heating the well, unsealing the well and flowing the mixture into a second well (which may contain a second substrate). At best, the Examiner's proposed combination might teach this process;⁶ however, this is very different from the claimed method, in which the mixture is flowed through each of the plurality of solid supports (step a), prior to the selective heating/dissociation (step b). The Examiner has not addressed this aspect of the claimed method and thus, a *prima facie* case of obviousness has not been established. Moreover, neither the cited references, nor the Examiner's proposed combination demonstrate how or why such an aspect could or should be implemented.

Appellants note that this particular feature of the claimed method has numerous advantages as it allows for simultaneous and rapid collection/separation/elution of different polynucleotides via a single serial arrangement. This arrangement allows for the complete starting volume of a sample to contact each solid support. Thus, the complete volume of a single sample can effectively be run “in parallel” on a single linear system by using the claimed method. In contrast, the devices and methods outlined by the Examiner require splitting up the sample

⁶ This assumes that there would be a reason to modify Zanzucchi in this manner, which does not appear to be the case.

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such that the entire sample does not contact each solid support because they either use combined parallel and serial systems or arrays for processing (such as Fig. 8A in Zanzucchi, which divide up starting material initially) or use their entire array as a parallel system, across which the sample is eventually evenly distributed (and thus less of the sample interacts with the binding partners, see e.g., Fig. 1, Okano and Fig. 2A, Brenner).

The presently claimed invention combines the advantages of serial flow (higher concentration/movement of the complete solution across/through each solid support, ability to recycle reagents along the flow path) with the advantages of parallel techniques (greater diversity of collection, accelerated processing speeds, etc) in a manner so that the advantages of each technique can be realized. This is clearly a superior aspect over the embodiments disclosed in the cited art (and suggested by the Examiner), which are not arranged for such a result and are not taught to be used in such a manner. Further advantages of various embodiments of this arrangement are discussed in the Application at page 25, line 17 to page 26, line 8 (and include, for example, the ability to use “excess” reagents that would have otherwise been wasted in a reaction).

In addition, Appellants note that there is no reason to modify the teachings of Zanzucchi to achieve the presently recited elements as presently claimed. In particular, it is noted that Zanzucchi already teaches devices (such as FIG. 7B and 8A) that are both parallel and serial. As such, it is clear that one of skill in the art would not have been motivated to modify Zanzucchi as described by the Examiner, as Zanzucchi outlines an alternative (and inconsistent) approach for addressing the issues solved by the presently recited claims.

Appellants note that the Examiner’s comments in the Advisory Action do not actually address the issues noted above. While most of the comments the Examiner made in the Advisory Action are similar to those noted above (and thus have been addressed), Appellants note that in lines 15-20 on page 2 of the Advisory Action, the Examiner found that Zanzucchi teaches an embodiment “without” valves. For support for this teaching, the Examiner has cited FIG. 12. As an initial point, Appellants note that FIG. 12 depicts a channel gate electrode (see col. 3, lines 59

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and 60), which is used to control the flow of the mixture; thus, this figure does not actually teach what the Examiner asserts it teaches. Moreover, even if some reference did teach a serial array without any type of flow control system, Appellants note that the present claims are still directed to a method and not a device. Thus, the relevant teaching that the Examiner must supply is for using the device in the manner claimed. This is not present (and as noted below, is even generally taught away from) in Zanzucchi.⁷

As the cited references and the proposed combination and modification thereof do not provide the recited element of “(b) after step (a)...”, not all of the elements have been taught and a *prima facie* case of obviousness has not been established with regard to Claim 21 and its dependent claims.

B. The Examiner has not Demonstrated that there Would be a Reasonable Expectation of Success in his Proposed Combination.

In the Final Office Action, the Examiner has asserted that “[i]n view of the well-developed state of the art, said ordinary artisan would have had a most reasonable expectation of success.” (Final Office Action, p. 6). However, the Examiner has not explained what this means or why that expectation would be there. Indeed, Appellants submit that, for at least some of Zanzucchi’s embodiments, it is clear there would not have been an expectation of success in the Examiner’s combination, as demonstrated by Zanzucchi itself.

As noted above, in Zanzucchi the flow of the mixture is controlled by the closing of valves in channels.⁸ Zanzucchi teaches that these valves are required for the device to function

⁷ Appellants note that there are some embodiments in Zanzucchi with separate flow paths that have a parallel relationship. These embodiments are not relevant as the parallel nature of these embodiments is due to the inclusion of parallel flow paths and is not achieved through the use of a single flow path with a plurality of supports through which a sample flows serially.

⁸ Appellants note that the valves appear to be important for those wells in which a temperature change is to occur. (See, e.g., Example 1).

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(or else the fluid leaves the chamber when heated)⁹. Appellants note that, in many embodiments, Zanzucchi teaches that the increase in temperature of the wells results in the sealing of the wells by the valves (col. 9, lines 38-54). Thus, it is clear from the teachings in Zanzucchi that, at least in some embodiments, elevated temperatures will keep wells closed and prevent a mixture from flowing out until the mixture cools. This would be problematic for the Examiner's proposed modification of Zanzucchi. In particular, if the wells include polynucleotides bound to a solid support, when that well is heated the well will become sealed.¹⁰ More importantly, the valves will not open until the solution cools. This is problematic for the Examiner's proposed combination because even though the heat may, temporarily, allow for the release of the polynucleotides, the mixture cannot be eluted out (as recited in step c of Claim 21) because the well is sealed. Additionally, as is known by those of skill in the art, cooling the mixture in the well will result in the rehybridization of the polynucleotide to the solid support, which will prevent the polynucleotide from flowing out once the valves are opened.

Indeed, Appellants note that the Examiner's comments in the Advisory Action further support the essential nature of the presence of the valve in Zanzucchi's device. In particular, the Examiner's proposed use of Zanzucchi appears to require the use of the valve in order to close the channel and thereby only heat one support without heating a following support.¹¹ Appellants note that the Examiner's comments regarding embodiments which lack a valve are moot, as FIG.

⁹ "Because of the high temperatures required in the last two steps, a significant vapor pressure may develop in the first well 36, causing a back pressure in both directions--back toward the sample loading channel 34 and forward to the succeeding second well 40. Thus preformed valves 62 and 63 as shown in FIG. 6A...are preloaded into the channel 38." (3rd paragraph, Example 1)

¹⁰ Appellants note that Zanzucchi does teach other valves; however, the Examiner has not supplied a reason for selecting the other valves and it is clear from the reference that the valves are not art recognized equivalents as they have different, and particular important, properties.

¹¹ See Advisory Action, page 2, lines 7-14, "...the temperature sensitive valve so Zanzucchi et al., allow this very requirement to be practiced."

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12 does not teach the absence of a valve in any of Zanzucchi's embodiments.¹² Rather, FIG. 12 appears to teach an electrode that is capable of controlling the flow rate from a reservoir (which does not appear to be heated) into the initial channel to "compensate for faster or slower movement of certain materials through the channels..." (Col. 14, lines 15 and 16). Read in its entirety, the section appears to be teaching that the electrodes can help slow or accelerate the flow, not that this device should be used in place of the explicitly taught valves, or that it could be used in conditions where heating and cooling were to be used (for which Zanzucchi teaches the use of valves).

In the Advisory Action, the Examiner has generally asserted that Okano remedies some of the failings of Zanzucchi, as Okano teaches an "electrode-specific" heating means. However, as noted previously, Okano does not teach the use of specific heat (e.g., at a specific location), but rather the use of general heat (e.g., throughout the solution) combined with specific electrical changes. The "heating means" in Okano is to the entire eluent solution, and thus would be across all of the device if used in a manner as described by the Examiner and taught by Okano (see, e.g., col. 3, lines 14-25, teaching a general heated eluent combined with an electric field, and col. 6, lines 5 & 6.) As such, if anything, Okano teaches elevating the temperature of all of the supports at once (even when combined in the manner described by the Examiner), and thus would not be combined in the Examiner's proposed combination, as the claims explicitly indicate that when one support is heated at least one other is not. As such, Okano's actual teachings do not remedy the issues noted above and do not suggest that one of skill in the art would have believed that the Examiner's proposed combination would have worked.

¹² If the Examiner intended to assert that a specific subset of some of the valve embodiments taught in Zanzucchi could be used in a specific combination with the other references, and then used in a specific manner to make the resulting method obvious, Appellants request that this asserted combination and reason to use these various embodiments be made of record so they can be addressed. Appellants note that the two valves (heat vs. electrically driven) cannot be considered to be art recognized equivalents.

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In light of the above issues, it is clear that, one of skill in the art would not have reasonably expected the asserted combination to work.

C. There are Significant Differences Between the Cited Art and the Claimed Invention

In addition to the specific differences between the Examiner's proposed combination and the presently claimed invention noted above, Appellants also note that, as a whole, there are significant differences between the teachings in the art and the claimed invention. Importantly, Appellants note the following: a) that there is no reason to modify Zanzucchi's explicitly taught method, b) that Brenner teaches away from the Examiner's proposed modification, and c) that there is no reason to combine Okano with the other references.

There is no Reason to Modify Zanzucchi's Method to a Method Involving Multiple Wells, Each having a Specific Solid Support.

Appellants note that there is no reason to modify the method taught in Zanzucchi's to include a method that employs multiple wells where each well has a different solid support (arranged in series) and then to use the device in the manner recited in the claims. Not only has no reason been supplied to make this modification, but the method that is taught in Zanzucchi (stepwise action on previously adjusted products) is at odds with the Examiner's proposed combination. For instance, Zanzucchi teaches that each well is a reaction site for the previous product (see, e.g., Example 1); in contrast, the presently claimed methods flow the entire initial mixture through all of the solid supports, where each solid support functions at that time to collect a specific polynucleotide (via a specific capture agent). Thus, how and when each of the wells in Zanzucchi functions is significantly different from how and when each of the recited solid supports function in the claimed method. While Appellants appreciate that general knowledge can be adequate to provide a reason to combine various elements; here, no such knowledge has been noted by the Examiner and the primary reference actually teaches a

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technique that is at odds with the other references it is to be combined with and at odds with the approach recited in the present claims.¹³ As such, Appellants respectfully submit that the Examiner has not supplied an adequate reason for why one of skill in the art would include multiple wells of different solid supports, in series, and then perform the claimed method (instead of simply the method recited in Zanzucchi). Appellants note that item 10 on page 4 of the Final Office Action appears to suggest that some possible combinations of Zanzucchi could include separate heating elements in each well; however, this does not suggest that the device should be used in a method as claimed.

Brenner Teaches Away from the Examiner's Proposed Combination

The Examiner has asserted that "it would have obvious... to have combined the microparticles of Brenner in the individual cells of the array of Okano, with the series of wells/array of Zanzucchi..." (Final Office Action, page 6). Appellants do not agree with this assertion.

The Examiner has attempted to combine or modify the teachings in Brenner, involving a process that is explicitly parallel, with a serial embodiment in order to obtain an element of the presently claimed invention (e.g., the "mixture flows serially through each of the plurality of solid supports"). Such a combination is improper as it would defeat the purpose of the array in Brenner and because Brenner teaches away from such a modification.

Brenner *explicitly* states that "[a]n important feature of my invention is the capability of applying the method to many different polynucleotides in parallel..." (col. 3, lines 46-62 of Brenner, emphasis added, *see also*, col. 2, lines 24-30; col. 4, lines 60-67; and col. 7, lines 10-20). Thus, Brenner actually teaches that his microparticles should be used in parallel

¹³ Again, Zanzucchi teaches the use of separate wells for a stepwise manipulation of an initial product, compared with the claimed invention, which involves the use of all of the solid supports in the first method step.

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applications and he teaches away from a serial (or purely linear) arrangement. As appreciated by the Examiner, it is improper to “combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983)” (M.P.E.P. §2145 (X)(D)(2)) or where the modification would change the principle of operation of the references.¹⁴ Not only does Brenner generally teach away from stepwise serial embodiments, but the application of Brenner’s microparticles in a serial application would remove the simultaneous/parallel aspect taught in Brenner as an important advantage of his invention. As such, the combination of Brenner with Zanzucchi as proposed by the Examiner, is clearly improper.

There is no Reason to Combine a) Okano and b) Brenner and/or Zanzucchi

Appellants note that the Examiner, while relying on Okano for some teachings, has identified no reason why one of skill in the art would have used the cited teachings of Okano in combination with Brenner and/or Zanzucchi. Appellants respectfully remind the Examiner that, in order to establish a *prima facie* case of obviousness, it is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. In the Final Office Action, no reason was provided as to why Okano should be combined with Brenner or Zanzucchi. As such, a *prima facie* case of obviousness has not been established.

Moreover, Appellants submit that there does not appear to be a reason to make the Examiner’s proposed combination of the microparticles of Brenner with the individual cells of Okano because the substrate (microparticles) in the Brenner reference would be redundant to the

¹⁴ “If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)” M.P.E.P. §2143.01.

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substrate (electrode surface) in the Okano reference. Because it would be redundant, one of skill in the art would not have been prompted to combine these aspects as asserted by the Examiner.

As such, the Examiner has failed to identify an adequate reason for combining the various components noted in the cited references. As such, a *prima facie* case of obviousness has not been established.

Errors of Law and Procedure

- The Examiner has improperly combined Brenner and Zanzucchi, as Brenner teaches away from the purely serial aspect cited in Zanzucchi.
- The Examiner has not addressed each of the pending claims. It appears as though the Examiner has primarily addressed Claim 21 on the merits, discounting elements in the dependent claims, such as methods involving simultaneous release of polynucleotides and where all of the liquid flows through each of the substrates. Rather than considering the claims on their merit, the Examiner appears to state that such things are simply an “obvious design choice.” However, the Examiner has supplied no support for this general assertion. Appellants note that such an “obvious design choice”, must be obvious for the issues that are pertinent to the cited art. Appellants note that the art cited by the Examiner is generally directed to microfluidic/microelectronic devices for the detection and/or manipulation of very small amounts of nucleic acid sequences. In contrast, the presently claimed device is directed to serial collection, and isolation of polynucleotides. There appears to be little or no reason why the technology in the references cited by the Examiner would benefit from the additional elements recited in the dependent claims. Thus, these dependent claims establish further points of nonobviousness over the cited art (some of which are addressed in detail below). Appellants request that support for the Examiner’s assertions be made of record (e.g., the Examiner can take official notice of such teachings) or withdraw the rejections of the dependent claims.

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- Appellants note that the Examiner's reference to the Appellants' own work (item 26, on page 8 of the Final Office Action) is improper, as the Appellants' disclosure cannot be used against them in demonstrating obviousness. The cited section only demonstrates that the Appellants appreciated the value of these variables for the claimed invention, and does not establish that, prior to the instant filing, anyone else would have necessarily understood these options or even the recited method.

Incorrect Factual Characterizations:

- FIG. 12 of Zanzucchi does not appear to teach an embodiment that does "not include a valve." Rather, FIG. 12 appears to depict a drain electrode that has a specific purpose at a specific part of the device (*see, e.g.*, col. 14, line 21-23). It does not appear to be taught as an alternative to the relevant valves.
- Okano does not teach the use of specific heat, but rather the use of general heat combined with specific electrical changes. Okano, at best, might teach that general heating of a sample combined with a change in electrical charge, can be used to assist in elution.
- Zanzucchi's teaching of wells arranged in a serial manner (and Zanzucchi's teaching of an "in-turn" use of each of those wells) does not teach a serial arrangement in which different solid supports (each with a specific capture probe) are arranged in series and that one should flow a sample through these prior to performing the step recited as step (b). Indeed, it is clear from the methods described in Zanzucchi that manipulations are to occur in each well in series (on the product from the previous well). Thus, even if one were to arrange the wells and solid supports as noted above (for which there is no teaching in the references or their combination), then, following the teachings of Zanzucchi, one would flow the sample into a first closed well, heat it, then flow it into the second closed well and heat it. This is clearly distinct from the claimed method in which the mixture flows through a plurality of solid supports before step (b) occurs.

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- Zanzucchi does not appear to teach that beads are present in each well. Zanzucchi, while teaching the option of paramagnetic beads in one well, does not teach the presence of solid supports (through which the mixture can flow) simultaneously in multiple wells that are arranged in series and are used in the claimed manner. Moreover, the “beads” in Zanzucchi are paramagnetic beads and appear to be used “to bind DNA material and to move the DNA to the succeeding wells for amplification, detection and assay”. (Col. 8, lines 28-34, emphasis added). As such, it appears that there would be no reason to use multiple sets of beads in each well because movement of the beads from the first well to the second well would place the beads in the second well.¹⁵
- The Examiner has mischaracterized the claimed invention on page 3 of the Final Office Action. The Examiner has interpreted the claimed invention as involving “...two different capture moieties...bound at two different locations on a support...”. In contrast, the claims recite that each support has “a sequence-specific capture agent complementary to a different-sequence polynucleotide...”. Thus, the claims clearly indicate that the different capture agents be present on different supports. The Examiner does not appear to have addressed this element in his rejections.
- The Examiner has mischaracterized the claimed invention on page 3 of the Office Action. The Examiner has interpreted the support as acting as a “flow path”. However, Appellants note that the claims clearly recite that this is not the case. Rather, the “flow path...[contains] a plurality of solid supports...” Appellants do note that the mixture also flows through the solid supports.

¹⁵ It is noted that col. 10, lines 6-10 describe an alternative embodiment in which PCR amplification occurs on paramagnetic beads. However, this is still a single well with beads, and as it occurs at the end (detection stage) would not motivate one to have multiple wells with beads each with a specific capture agent.

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Additional Distinctions Present in the Dependent Claims.

In addition to the arguments noted above, Appellants note that many of the dependent claims recite further elements that are not be obvious in light of the Examiner's proposed combination. Exemplary of such elements are addressed below.

Claim 22: The method of claim 21, wherein said altering further comprises selectively heating a second solid support to release bound polynucleotides therefrom, to allow preferential elution of the polynucleotides released from the second solid support.

In addition to the issues noted above, Appellants note that Claim 22 is nonobvious over the cited art for additional reasons. For example, Claim 22 recites that the "altering" step (step (b)) further comprises heating a second solid support to release the polynucleotides bound to that support. Thus, Claim 22 includes the following: running a mixture through at least two solid supports (where each solid support has a different capture agent); then heating one of the solid supports to elute the polynucleotides associated therewith; heating the second solid support to elute the set of polynucleotides associated with the second solid support; and finally eluting the released polynucleotides such that the eluted polynucleotides are isolated in separate form. As this step of selectively heating a second solid support is not taught by the cited art, Appellants submit that not all of the elements have been taught and a *prima facie* case of obviousness has not been established.

Claim 23: The method of claim 22, wherein heating of the first and second supports is performed simultaneously, and the polynucleotides released thereby are eluted in separate form, without mixing with each other

As noted above, Zanzucchi teaches the stepwise treatment of the wells located in series in a single flow path. Thus, Zanzucchi teaches a method in which one manipulates a solution in a first well and then moves the solution to a next well for a subsequent manipulation. In contrast, Claim 23 is directed to a method where a plurality of solid supports, in a series, are heated

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simultaneously to achieve a desired elution (such that the “eluted polynucleotides can be isolated in separated form”). It does not appear as though the Examiner has addressed this element and furthermore, it does not appear as though there is any reason or teaching in Zanzucchi or the other cited references to support the use of such a step in their devices or methods. As such, Appellants submit that the claim is nonobvious over the Examiner’s proposed combination.

Claim 30: The method of Claim 21, wherein all of the mixture flows through every one of the solid supports as the mixture proceeds down the flow path

Appellants note that the elements in Claim 30 result in a method in which the entirety of the mixture flows through each of the solid supports; thereby ensuring that as much of the mixture is screened as possible prior to the mixture passing out of a solid support and into the next solid support. This results in a significant advantage over other possible methods. For example, as noted in the specification, this combination allows for any reagents or other substances to be “recycled” by flowing the reagents through the flow path through each of the solid supports. This effectively allows for the “reuse” of any raw materials in each of the solid supports, while increasing the degree of interaction between the raw materials and the polynucleotides associated with the solid supports, and still keeping each of the polynucleotides in a separate section.¹⁶ Finally, while such an arrangement is possible for the presently claimed method (which is directed to a method of separation), it does not appear to be readily feasible in the teachings of Brenner (because sample trapped on the inside the solid support would not be viewable by the detection system, see FIG. 3 of Brenner) and Okano (because there does not seem to be a way to flow a sample through the electrodes in Okano, which are planar and require electrical contact to work (see, FIG. 2, 3, and 6). Appellants note that Claims 31-33 have a similar feature.

¹⁶ Appellants note that the advantage of “reusing” raw materials in this manner also applies to other serial arrangements where there are two or more solid supports (e.g., Claim 21).

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Claims 34: The method of Claim 21, wherein the flow path is defined by a column.

Similarly, Claim 34 recites aspects that yield advantageous results for the purification aspects of the presently claimed method, but are, relatively speaking, inapplicable to the microelectronic devices (Okano and Zanzucchi) and two-dimensional arrays (Brenner and Okano) cited by the Examiner. Indeed, the function and use of the arrangements in Okano, Brenner, and Zanzucchi would teach away from cylindrical arrangements. For example, because these references are directed to detecting or collecting very small amounts of a target sample, it is generally beneficial to place the observing or collecting device as close to the molecule that it is detecting or collecting (which is frequently achieved by using a flat surface (*see, e.g.*, Zanzucchi, FIG: 1A, well 40, 4A-5B; Okano, FIG. 1 and 6; and Brenner, FIG. 3). In such embodiments, a thin or shallow flow path is desirable (as shown in all of the depicted embodiments in the cited art) in order to minimize sample volume. In contrast, a column arrangement, as recited in the claim, would prevent one from forming a two dimensional array (as taught in Okano and Brenner) and would require additional volume between the target and the detector. Thus, there is no reason for modifying the above references into a column format, and such a configuration would generally be considered undesirable for the stated goals in the cited references. Appellants note that Claims 35-37 have a similar feature. Appellants note that column format does have advantages for the claimed methods, which are directed to methods of isolating polynucleotide sequences. For example, the cylindrical format allows for greater volumes to be processed.

As these elements clearly reflect patentable distinctions over the cited art, the dependent claims are entitled to a proper examination by the Examiner.

VIII. CONCLUSION

Because not all of the elements have been taught, the Examiner has not demonstrated that one of skill in the art would have reasonably expected the combination to work, and the Examiner has not identified proper or sufficient reasons to combine the cited references, a *prima*

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facie case of obviousness has not been established. As such, Appellants request that the rejection be withdrawn and the claims allowed.

IX. SUMMARY OF CLAIMS APPENDIX

Attached hereto as Appendix A is a copy of the finally rejected claims in the present case.

X. SUMMARY OF EVIDENCE APPENDIX

No evidence is being submitted with the present appeal brief.

XI. SUMMARY OF RELATED PROCEEDINGS APPENDIX

No related appeal proceedings are known.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.



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APPENDIX A
(Claims as Entered after Advisory Action)

1. — 20. (Canceled)

21. A method for isolating one or more different-sequence polynucleotides from a mixture, the method comprising:

(a) flowing the mixture through a flow path containing a plurality of solid supports which are located in series in the flow path, such that the mixture flows serially through each of the plurality of solid supports, each support having bound thereto a sequence-specific capture agent complementary to a different-sequence polynucleotide, under conditions effective to specifically bind different-sequence polynucleotides to corresponding sequence-specific capture agents on one or more of the supports,

(b) after step (a), releasing bound polynucleotides from a selected support by altering a physical property of that support while leaving unaltered the same physical property of at least one other of the supports, wherein the physical property is temperature, and wherein said releasing is accomplished by heating a first solid support; and

(c) eluting the released polynucleotides through the flow path such that the eluted polynucleotides can be isolated in separated form.

22. The method of claim 21, wherein said altering further comprises selectively heating a second solid support to release bound polynucleotides therefrom, to allow preferential elution of the polynucleotides released from the second solid support.

23. The method of claim 22, wherein heating of the first and second supports is performed simultaneously, and the polynucleotides released thereby are eluted in separate form, without mixing with each other.

24. The method of claim 21, wherein (i) the polynucleotide mixture comprises a plurality of different polynucleotide populations, each different polynucleotide population comprising a plurality of different polynucleotides that contain a distinct sequence associated with that population, and (ii) different sequence-specific capture agents on the different solid supports are complementary to different polynucleotide populations in the mixture.

25. The method of claim 21, wherein the polynucleotide mixture comprises a plurality of sequencing ladders.

26. The method of claim 21, wherein the polynucleotide mixture comprises a plurality of PCR products.

27. The method of claim 21, wherein the polynucleotide mixture comprises a plurality of ligation products.

28. The method of claim 21, wherein the different-sequence polynucleotides in the mixture include recovery tags for which the capture agents are complementary.

29. The method of Claim 21, wherein all of the solid supports in the flow path are located sequentially in the flow path.

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30. The method of Claim 21, wherein all of the mixture flows through every one of the solid supports as the mixture proceeds down the flow path.

31. The method of Claim 21, wherein the solid support has an external surface and the flow path is defined by a structure having an internal surface, and wherein the external surface of the solid support abuts the internal surface of the flow path so that the mixture flows through the solid support in order to proceed down the flow path.

32. The method of Claim 21, wherein the solid support has an external surface and the flow path is defined by a structure having an internal surface, wherein the external surface of the solid support is immediately surrounded by the internal surface of the structure defining the flow path.

33. The method of Claim 21, wherein the solid support has an external surface and the flow path is defined by a structure having an internal surface, wherein the structure defining the flow path is a cylindrical tube made of heat-shrinkable plastic, and wherein the heat-shrinkable plastic immediately surrounds the external surface of the solid support.

34. The method of Claim 21, wherein the flow path is defined by a column.

35. The method of Claim 34, wherein the column is a cylindrical column.

36. The method of Claim 35, wherein the solid support is a cylindrically shaped frit.

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37. The method of Claim 36, wherein an external surface of the cylindrically shape frit is immediately surrounded by an internal surface of the column so that all of the mixture flows through the solid support in order to proceed down the flow path.

38. The method of Claim 21, wherein the heating of the solid support is achieved via a heating element that enwraps the solid support.

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**APPENDIX B
EVIDENCE APPENDIX**

No evidence is being submitted in the present appeal brief.

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**APPENDIX C
RELATED PROCEEDINGS APPENDIX**

No related appeal proceedings are known.